REMARKS/ARGUMENTS

Claims 1, 5-7, 9, 11 and 27 are presently pending. The present reply includes amendments to claims 1 and 6 and cancellation of claim 5. Reconsideration of this application and entry of the amendments after final are respectfully requested.

The amendments place the claims in better form for appeal. Additionally, the amendments address items brought up by the examiner in the final office action.

By these amendments and claim cancellation, Applicant does not acquiesce to the propriety of any of the Office's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 USPQ.2d 1865 (US 1997). Furthermore, Applicant reserves the right to file continuing applications directed to the subject matter of any claim amended or cancelled for any reason.

In view of the amendments and following remarks, favorable consideration and allowance of the application is respectfully requested.

I. Withdrawal of 35 U.S.C. § 112 Rejection

The Applicant notes with appreciation the Examiner's withdrawal of the rejection of claim 1 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Office Action mailed October 30, 2008 ("OA"), page 3.

II. 35 U.S.C. § 103 Rejections

Claims 1, 5-7, 9, 11 and 27 stand rejected under 35 USC § 103(a) as allegedly unpatentable over U.S. Patent No. 5,464,650 ("Berg") in view of Su *et al.*, J. Clinical Investigation, 1999, cited on PTO Form 1449 ("Su"). Applicant respectfully traverses.

To maintain a proper rejection under 35 U.S.C. § 103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show

that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

According to the Office, Berg "is directed to an intravascular stent. The invention allows for the sustained release of the drug to vascular tissue.... Many different agents can be utilized. One particular example [is] anti-inflammatory agents." OA, page 4 (emphasis in original).

The Office acknowledges that Berg "does not specify that the therapeutic substance is rosiglitazone." OA, page 5. The Office asserts, however, that this deficiency is cured by Su because Su "indicates that PPARγ agonists reduce colonic inflammation" and because "BRL 49653 (rosiglitazone) exhibits a highly significant anti-inflammatory effect." OA, page 5 citing Su, page 33, last paragraph. Based on these interpretations of Berg and Su the Office concludes that,

> [i]t would have been obvious to one of ordinary skill in the art to have combined ... Berg ... and Su ... and utilize rosiglitazone as the therapeutic

> substance. One of ordinary skill in the art would have been motivated to select rosiglitazone as Berg ... indicates that anti-inflammatory are suitable therapeutic agents to be utilized in the stent coating and Su ... indicates that rosiglitazone exhibits significant anti-inflammatory effect. Furthermore, the selection of a specific drug is considered to be prima facie obvious depending on the desired condition/symptoms to be treated.

OA, page 5. The Office goes on to state that,

> [a]bsent any evidence to the contrary ... there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

OA, page 5 (*sic*). Applicant respectfully disagrees.

A. Su is not Analogous Art so there is no Motivation to Combine

As stated above, the Office argues that, "[i]t would have been obvious to one of ordinary skill in the art to have combined ... Berg ... and Su ... and utilize rosiglitazone as the therapeutic substance." OA, page 5. This position is incorrect, however, because Su is not analogous art to Berg and as a result, there is no motivation to combine these references.

Determining whether art is analogous and appropriate to combine under 35 U.S.C. § 103 involves a two-part inquiry. First, to be analogous, the art must be "within the field of the inventor's endeavor." *In re Deminski*, 796 F.2d 436, 442 (Fed. Cir. 1986). If the art is outside the inventor's field of endeavor, art is only analogous if it is "reasonably pertinent to the particular problem with which the inventor was involved." *Id.* References are selected as being reasonably pertinent to the problem based on the judgment of a person having ordinary skill in the art. *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992)("[I]t is necessary to consider 'the reality of the circumstances,' – in other words, common sense – in deciding in which fields a person of ordinary skill would reasonably be expected to look for a solution to the problem facing the inventor."); *see also In re Wood*, 599 F.2d 1032, 1036 (C.C.P.A. 1979). These tests define the prior art

relevant for the obviousness determination, and are meant to defend against hindsight reconstruction. *See id.*; *In re Clay*, 966 F.2d 656, 659-60 (Fed. Cir. 1992).

1. Berg and Su are not within the Same Field of Endeavor

The inventor's field of endeavor is determined from "the scope explicitly specified in the background of the invention." *In re Wood*, 599 F.2d 1032, 1036 (C.C.P.A. 1979). Here, the background of the invention of Berg states,

- It is ... an object of the present invention to provide a stent having a therapeutically significant amount of a drug applied thereto.
- It is also an object of the present invention to provide a stent which may be delivered and expanded in a selected blood vessel without losing a therapeutically significant amount of a drug applied thereto.
- It is also an object of the present invention to provide a drug-containing stent which allows for a sustained release of the drug to vascular tissue.
- It is also an object of the present invention to provide a simple method for applying to a stent a coating of a therapeutic substance.

See Berg, Col. 2, ll. 13-26. Thus, Berg's field of endeavor relates to providing a stent with a therapeutically significant amount of a drug applied thereto.

Su relates to the study of PPAR-γ in the colonic epithelium to ascertain its potential role in colonic inflammation and inflammatory bowel disease. *See* Su, Abstract and page 383, last paragraph. The study of the mechanisms of inflammatory bowel disease is not within the same field of endeavor as Berg's endeavor of providing a stent with a therapeutically significant amount of a drug applied thereto as there is no discernable overlap between these endeavors. Therefore, under this first prong of the "motivation to combine" test there is no motivation to combine these references.

2. Su is not Reasonably Pertinent to the Particular Problem Addressed by Berg

As stated in the Background of the Invention, the particular problem addressed by Berg was how to keep a therapeutically significant amount of a substance on the metal of a stent. Particularly, Berg states,

> Metal stents such as those disclosed in U.S. Pat. No. 4,733,665 issued to Palmaz, U.S. Pat. No. 4,800,882 issued to Gianturco or U.S. Pat. No. 4,886,062 issued to Wiktor could be suitable for drug delivery in that they are capable of maintaining intimate contact between a substance applied to the outer surface of the stent and the tissues of the vessel to be treated. However, there are significant problems to be overcome in order to secure a therapeutically significant amount of a substance onto the metal of the stent; to keep it on the stent during expansion of the stent into contact with the blood vessel wall; and also controlling the rate of drug delivery from the drug on the stent to the vessel wall.

Berg, Col. 2, ll. 1-12. Following *In re Oetiker*, one of ordinary skill in the art would be required to consult Su, relating to the role of PPAR-γ in the colonic epithelium and inflammatory bowel disease, to address the problem of securing a therapeutically significant amount of a substance onto the metal of a stent. 977 F.2d 1443, 1447 (Fed. Cir. 1992). Considering the "reality of the circumstances" as required by *In re Oetiker*, Su is not reasonably pertinent to the particular problem addressed by Berg. Accordingly, under this second prong of the "motivation to combine" test there also is no motivation to combine Berg with Su.

3. Common Mention of Anti-Inflammatory Agents Does Render Berg and Su Analogous Art Suitable for Combination

As stated above, Berg and Su are not analogous art under the relevant tests and are not appropriate to combine under 35 USC § 103. The fact that each discusses anti-inflammatory agents in some capacity does not change this result. The teaching of *Monarch Knitting* is illustrative.

In *Monarch Knitting*, the Federal Circuit held that in applying the two-step test to determine whether art is analogous, it is error to define "the problem in terms of its solution" because this involves "improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH,* 139, F.3d 877 (Fed. Cir. 1998). Stated another way, the common mention of an element or solution does not serve to bring references into a common field of endeavor. *See, for example, In re Clay*, 966 F.2d at 659 ("[The reference] cannot be considered to

be within [the inventor's] field of endeavor merely because both relate to the petroleum industry."); *United States Surgical Corp. v. Hospital Products International PTY Ltd.*, 701 F. Supp. 314 334 (D. Conn. 1988) ("The evidence indicates that the paper stapling art is not one that would lend itself to the resolution of the problems encountered in surgical stapling...."); *Schneider (Europe) AG v. SciMed Life Systems, Inc.*, 852 F. Supp. 813, 853 (D. Minn. 1994) *aff'd*, 60 F.3d 839 (Fed. Cir. 1995) (unpublished), *cert. denied*, 516 U.S. 990 (1995) ("Combining devices that have a short guide wire lumen, but are not used in dilation or coronary dilation, with ... Percutaneous Transluminal Coronary Angioplasty devices that have a long guide wire lumen, would not have been obvious to one of ordinary skill because they would not have been reasonably pertinent to the particular problem with which [the inventor] was concerned."). Accordingly, there is no motivation to combine Berg with Su.

B. There is No Suggestion to Make the Claimed Invention

The present claims recite a site-specific drug delivery medical device having a coating consisting essentially of rosiglitazone and at least one biocompatible polymer wherein said site-specific drug delivery device is a stent.

Berg discloses corticosteroids, aspirin and the broader term "anti-inflammatories" as potential therapeutic agents to apply to a stent. The broad term "anti-inflammatories" encompasses hundreds, if not thousands, of compounds as this term includes steroidal anti-inflammatory agents including corticosteroids, non-steroidal anti-inflammatory agents, certain anti-proliferative agents, certain prostaglandin inhibitors, certain PPAR-γ inhibitors, certain immunosuppressive agents, and others. Berg does not disclose which type of anti-inflammatories, other than glucocorticoids are appropriate to be used with the claimed stent. Importantly, an invention is not invalid for obviousness if the inventor would have been motivated "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art

gave ... no direction as to which of many possible choices is likely to be successful." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007).[1]

While Applicant does not dispute that Su discusses rosiglitazone and its potential role in inflammatory bowel disease, the combination of Su and Berg does not suggest a benefit of placing rosiglitazone and at least one biocompatible polymer on a stent.

C. There is No Reasonable Expectation of Success.

As stated *supra*, Berg merely discloses the broad term "anti-inflammatories" and several specific glucocorticoids. Berg does not provide any guidance for the use of other types of anti-inflammatory agents. The term "anti-inflammatories" encompasses hundreds, if not thousands, of compounds. There is no guidance in Berg as to which of these compounds, or classes of compounds, is appropriate for use in Berg's stent.

Su also does not provide a reasonable expectation of success for applying rosiglitazone and at least one biocompatible polymer to a stent including a vascular stent or a biliary stent. As stated, Su relates to the role of PPAR-γ in the colonic epithelium to ascertain its potential function and role in colonic inflammation and inflammatory bowel disease. Su provides data that in this environment rosiglitazone may be an effective anti-inflammatory compound and that rosiglitazone may alter

[1] *See also Ex Parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. & Interferences 1985) ("Presuming arguendo that the references show the elements or concepts urged, the Examiner presented no line of reasoning as to why the artisan reviewing only the collective teachings of the references would have found it obvious to selectively pick and choose various elements and/or concepts ... to arrive at the claimed invention. In the instant application, the Examiner has done little more than cite references to show that one or more elements or some combination thereof, when each is viewed in a vacuum, is known. The claimed invention, however, is clearly directed to a combination of elements. ... Based on the record, the artisan would not have found it obvious to selectively pick and choose elements or concepts from the various references so as to arrive at the claimed invention without using the claims as a guide."); *Ex Parte Chicago Rawhide Manufacturing Company*, 226 U.S.P.Q. 438 (Pat & Trademark Office Bd. App. 1984) ("The mere fact that a worker in the art could rearrange the parts of the reference device to meet the terms of the claims on appeal is not, by itself, sufficient to support a finding of obviousness. The prior art must provide a motivation or reason for the worker in the art, without the benefit of the appellant's specification, to make the necessary changes in the reference device.").

elements common to certain inflammatory pathways. Su, page 388, first paragraph. Su also provides, however, that rosiglitazone does not have the same effects in different physiological environments. Particularly, Su states that,

> We show that 2 different classes of ligands for PPAR-γ potently inhibit cytokine expression in 2 different PPAR-γ–expressing colon cell lines (21, 24). The increased potency of 15d-PGJ_2 relative to BRL 49653 contrasts with the direct binding affinities of these compounds for PPAR-γ, but is consistent with the relative potencies of these compounds for negative regulation of genes involved in the inflammatory response (12, 13). At present, it is not known why the EC_{50} for BRL 49653 is greater than that for 15d-PGJ_2. It is possible that cofactors necessary for transcriptional repression interact with ligand-bound PPAR-γ differently than those involved in transcriptional activation (42). We also do not exclude the possibility that these compounds inhibit cytokine gene expression through additional mechanisms independent of PPAR-γ. Indeed, a PPAR-γ–independent pathway may be operative in neuronal cells, where investigators have recently shown that 15d-PGJ_2 inhibits inducible nitric oxide synthase (iNOS) expression and promoter activity by inhibiting transcriptional activation via NF-κB (43). iNOS expression in microglial cells was not inhibited by TZDs, and the nuclear translocation and DNA-binding activities of NF-κB were unaffected by 15d-PGJ_2. <u>These results, however, are distinctly different from our findings in intestinal cell lines, where BRL 49653 does inhibit IL-8 expression</u>. Furthermore, we show that in Caco-2 cells, 15d-PGJ_2 inhibits the nuclear translocation and subsequent DNA binding of NF-κB via an IκB-α–dependent pathway by inhibiting the immune response–induced degradation of IκB-α. This is also distinct from the putative non-PPAR pathway of iNOS regulation in neuronal cells.

Su, page 387, last paragraph – page 388 first paragraph (emphasis added). This passage demonstrates that rosiglitazone has different effects in different physiological environments and that its mechanisms of action are not completely understood. Accordingly, there is no reasonable expectation of success based on Su that rosiglitazone will have similar effects in a physiological environment of stent placement vs. its effects in a colonic environment vs. its effects in a neural environment. Accordingly, the combination of Berg and Su does not provide a reasonable expectation of success.

For all of the reasons provided above, Applicant respectfully requests that the Examiner reconsider and withdraw the pending rejections of claims 1, 5-7, 9, 11 and 27 under 35 U.S.C. § 103.

III. Double Patenting

Claims 1, 5-7, 9, 11 and 27 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-26 of copending application No. 11/383,262 and also stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 15-18 of copending application No. 11/619,122 in view of Berg and in further view of Su. Applicant respectfully traverses.

The Office has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) or § 1.321(d) may be used to overcome an actual or provisional rejection based on non-statutory double patenting grounds. Without addressing the propriety of the Office's rejection, and specifically the Office's interpretation of what the cited references teach or suggest, Applicants respectfully and properly defer addressing the present rejections until there is otherwise allowable subject matter in each application. Only then is it proper to assess the propriety of the Office's rejections in view of the potentially allowable claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejections or that the rejections be held in abeyance until claims 1, 5-7, 9, 11 and 27 are allowable in the present application, and/or claims are allowable in copending Application Nos. 11/383,262 and 11/619,122.

CONCLUSION

For the foregoing reasons, Applicant believes all the pending claims are in condition for allowance and should be passed to issue. The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. 1.17, or credit any overpayment, to Deposit Account No. 01-2525. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at telephone (707) 543-5021.

Respectfully submitted,

/Alan M. Krubiner, Reg. No. 26,289/
Alan M. Krubiner
Registration No. 26,289
Attorney for Applicant

Medtronic Vascular, Inc.
3576 Unocal Place
Santa Rosa, CA 95403
Facsimile No.: (707) 543-5420

K:\195128\00014\20303_CRW\20303O22E2